REMARKS

In the April 24, 2006 Office Action, the Examiner rejected claims 38 and 42-43 under 35 U.S.C. §103(a) as allegedly obvious over Liu et al., J. Inorganic Biochemistry 1998, Vol. 71, pp. 1-6 (hereinafter "Liu") in view of Pisanti et al., Marine Pollution Bull. 1988, Vol. 19, pp. 328-333 (hereinafter "Pisanti"). Specifically, the Examiner alleges that Liu teaches that the presence of copper (II) metal would competitively bind with a DNA molecule intercalated with fluorescent ethidium dye. Further, the Examiner alleges that Liu discloses the binding constant of the copper as being around 10^{-10} (M^{-1}), which allegedly falls within the micromolar range. The Examiner also alleges that although Liu does not explicitly teach the inhibition of dissociation of the dye on DNA as an indication of the presence of metal, Pisanti teaches the presence of metals in the ecosystem. It is alleged that one of ordinary skill in the art at the time the invention was made would have been motivated by Liu to measure the presence of copper in an aquatic sample as taught by Pisanti.

Applicants respectfully disagree with the Examiner's rejection.

First, Applicants submit that the Examiner is engaging in hindsight reconstruction, which is not permissible in framing an obviousness-type rejection.

Upon examination of the Liu reference, one of ordinary skill in the art would appreciate that the binding experiments undertaken by Liu were performed on copper compounds under controlled conditions. At page 2, column 2, line 12, Liu outlines that the Cu^{2+} compounds were dissolved in Tris-HCl buffer. This indicates that experiments were undertaken at constant pH values and salt concentrations. Furthermore, all copper solutions were kept in the dark until utilized in the binding experiments in order to stop degradation. One of ordinary skill in the art would realize that the results of the binding experiments could not be directly applied to

environmental samples, because of wide variations in the salt concentrations, pH values and other factors related to such environmental samples. As indicated by Pisanti at page 329, line 12, although heavy metals may have harmful effects, the toxicity threshold of each individual metal is very variable and depends on the state of oxidation or of complexation of the metal. Further, many aquatic samples may also contain other contaminants or competitive agents that may effect the results of the binding experiments disclosed by Liu.

Therefore, the binding constant calculated by Liu, which putatively falls into the range of micromolar, could not be applied to environmental samples because of the controlled conditions under which it was calculated. One of ordinary skill in the art would be unable to ascertain that micromolar amounts of a toxicant comprising a metal atom in aquatic, terrestrial, gaseous or industrial environmental samples could be detected by the binding assay disclosed by Liu.

Second, Applicants submit that the combination of Liu and Pisanti, as suggested by the Examiner in the outstanding Office Action, is not supported by any suggestion or motivation in the prior art, nor by any reasonable expectation of success.

On one hand, Liu discloses a fluorescence quenching assay that can only be utilized for detecting interaction or binding between DNA and the copper (II) macrocyclic complexes specifically disclosed in Figure 1 of Liu, but not for other metal complexes or metal ions in general. Liu specifically indicates that certain structural characteristics of the copper (II) macrocyclic complexes, such as the presence of the macrocyclic groups therein and the square-planar configuration of the complexes, allow such copper (II) macrocyclic complexes to intercalate into the DNA double helix (see Liu, page 4, left column, lines 11-15). This in turn causes efficient replacement of the DNA-bound ethidium to be detected by fluorescence quenching (see Liu, page 4, left column, lines 21-24). Liu does not teach or even suggest that

other metal compounds, or metal ions in general, can also intercalate into the DNA to cause sufficient replacement of the DNA-bound ethidium that can be detected by fluorescence quenching.

On the other hand, Pisanti discloses the effect of various heavy or transitional ions or radicals (including copper ions or radicals) on microorganism aging. Specifically, Pisanti tested microorganisms grown in a cultural medium enriched with chloride salts of various metals, including copper (see Pisanti, page 328, Materials and Methods). Nevertheless, Pisanti does not teach or suggest that the heavy or transitional metal ions or radicals are complexed with any macrocyclic groups, or have similar structural characteristics to the copper (II) macrocyclic complexes disclosed by Liu.

Accordingly, one of ordinary skill in the art would appreciate that there is no reasonable expectation of success that the fluorescence quenching assay disclosed by Liu can be used for detecting the heavy or transitional metal ions or radicals disclosed by Pisanti.

Finally, Liu states that it has been difficult in the past to determine the binding constants of conventional metal complexes to DNA, because the binding of conventional metal complexes with DNA results in very small changes in the absorption spectra (see Liu, page 2, left column, lines 6-10). It is respectfully submitted that such a statement teaches away from using fluorescence quenching assays for studying other metal complexes.

In light of the above, Applicants respectfully submit that the claimed invention, as positively recited by claims 38 and 42-43 of the present application, is not obvious over Liu in view of Pisanti.

In the outstanding Office Action, the Examiner also rejected claims 44 and 45 under 35 U.S.C. §103(a) as allegedly obvious over Liu in view of Pisanti and further in view of U.S.

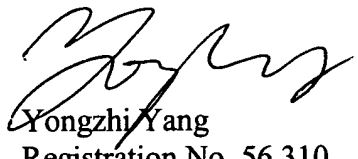
Patent No. 6,242,246 to Gold et al. (hereinafter "Gold"). The Examiner alleges that for the reasons outlined hereinabove, claims 44 and 45 are obvious over Liu in view of Pisanti. The Examiner further alleges that Gold teaches an efficient and sensitive screening technique for DNA binding agents by immobilizing DNA on a solid support and measuring the change of dye for an indication of the presence of the binding agent.

As submitted hereinabove, none of the cited references disclose the detection of micromolar amounts of toxicant comprising a metal atom by the dissociation of binding between a nucleic acid and a fluorescence dye. The disclosure of Gold relates to detection of a molecule that base pairs with immobilized DNA, while the claimed invention of the present application does not disrupt base pairing but rather changes the structure to sufficiently perturb the fluorescence of the dye.

Therefore, Applicants respectfully submit that the claimed invention of the present application is not obvious over Liu in view of Pisanti and Gold.

Based on the foregoing, Applicants correspondingly request withdrawal of the rejections against claims 38 and 42-45 and issuance of a Notice of Allowance.

Respectfully submitted,



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